

Review of the Draft NICEATM-ICCVAM Five-Year Plan

By the
SACATM Working Group for the NICEATM-ICCVAM Five-Year Plan
(FYPWG)

Submitted by:

Richard A. Becker, Ph.D., chair; Mary Jane Cunningham, Ph.D.; Helen E. Diggs, D.V.M., DACLAM; A. Wallace Hayes, Ph.D., D.A.B.T; and Martin L. Stephens, Ph.D.

Charter:

The SACATM Working Group for the NICEATM-ICCVAM Five-Year Plan (FYPWG) was formed in May 2007. Its purpose was to review how well this Plan addressed the following objectives: (1) research, development, translation, and validation of new and revised non-animal and other alternative assays for integration into federal agency testing programs and (2) identification of areas of high priority for new and revised non-animal and alternative assays for replacement, reduction, and refinement (less pain and distress) of animal tests. For each objective, the Plan was critically analyzed for what was presently being done and what was planned and how well these activities matched the above objectives. The review contained a critique of whether all present and planned activities were streamlined and necessary and what activities or gaps of knowledge were missing.

The enclosed report is a compilation of critical comments from the FYPWG. Members of the FYPWG were Richard A. Becker, Ph.D. (Chair), Mary Jane Cunningham, Ph.D., Helen Diggs, D.V.M., A. Wallace Hayes, Ph.D., D.A.B.T., and Martin L. Stephens, Ph.D. The report contains four sections: the charter of the FYPWG, a synopsis of the Five-Year Plan, and the review of the Plan divided into two sections, general comments and specific comments. Each of the review sections contains all comments from the FYPWG.

Synopsis:

A Five-Year Plan covering the period of 2008 to 2012 was prepared by NICEATM and ICCVAM in response to requests by the U.S. House of Representatives and Senate Appropriations Committees. The Plan identifies four challenges:

- a) to identify priority areas and facilitate the activities associated with these areas,
- b) to incorporate innovative research initiatives which will lead to new alternative test methods,
- c) to encourage acceptance and approval of alternative test methods to reduce, replace, or refine the use of animals (including issues involving their pain and distress),
- d) to develop and strengthen both national and international partnerships to facilitate the progress of the activities addressed in a) to c).

NICEATM and ICCVAM, through previous priority setting activities, have identified priority areas including ocular toxicity, acute toxicity, biologics, dermal toxicity, immunotoxicity, endocrine disruption, pyrogen testing, and chronic toxicity/carcinogenicity.

FYPWG Review – Introduction

The draft five-year plan represents an important opportunity and challenge for NICEATM, the ICCVAM committee itself, the 15 federal agencies represented by ICCVAM, and stakeholders from diverse sectors and perspectives. There is growing interest across all sectors for catalyzing more meaningful and rapid progress in the U.S. government for research to develop alternative methods, for lab investigations to validate

alternative methods, and for regulatory frameworks to adopt validated alternatives. As was pointed out at the ISRTP 2005 Workshop (Progress and Barriers to Incorporating Alternative Toxicological Methods in the U.S.¹), “...across the scientific, regulatory and stakeholder communities, there is a lack of understanding of the breadth and depth of ongoing efforts in the U.S. of research now in progress on alternative methods. This has arisen because, in the U.S., alternatives research is not housed in a single entity nor described in an agency’s communication or budget as specifically focused on development, standardization or validation of alternative methods. ... it would be very beneficial to have a nationally coordinated effort to gather this type of information and to disseminate it widely.”

The FYPWG recognizes that ICCVAM is a coordinating committee, and NICEATM’s role is to administer the ICCVAM and provide scientific and operational support for ICCVAM-related activities. Coordination and facilitation of activities across diverse federal agencies creates many challenges.

The activities of NICEATM and ICCVAM provide an unprecedented opportunity for (1) building upon federal agency and private sector research and development of new, revised and non-animal alternative assays; (2) coordinating and facilitating method translation and validation; and (3) promoting integration of these validated methods into federal agency testing programs. We believe the Five-Year Plan, once finalized, can serve ICCVAM, its 15 federal agencies, and stakeholders by providing a clear articulation of the vision and primary objectives of NICEATM/ICCVAM for the next five years.

FYPWG Review – General Comments:

Is the Draft Five-Year Plan Comprehensive?

The FYPWG appreciates the efforts of ICCVAM representatives and NICEATM staff in developing the Draft Five-Year Plan. The Draft Five-Year Plan provides an impressive compilation of ongoing research and development activities and method standardization studies being conducted or managed by the 15 ICCVAM federal agencies. In addition, the Draft Five-Year Plan contains information on method-development activities in Europe and Japan. There is no doubt that the molecular biology revolution, as exemplified by high-throughput and high-content screening methods, will soon sweep into the realm of regulatory testing and decision making. However, no matter how promising such methods may be, before they can be actualized in federal agency programs they will need to be validated (as require by the ICCVAM Authorization Act of 2000, 42 U.S.C 285I-3). Taken as a whole, these activities, which are laid out in the Draft Five-Year Plan, indicate the essential role NICEATM must play in order to administer ICCVAM activities. The sheer volume of activities, the complex scientific and technical challenges, and the exacting standards required for method validation exemplifies why there is now, more than ever, a need for ICCVAM and NICEATM to

¹ Becker RA, Borgert CJ, Webb S, Ansell J, Amundson S, Portier CJ, Goldberg A, Bruner LH, Rowan A, Curren RD, Stott WT. Report of an ISRTP workshop: progress and barriers to incorporating alternative toxicological methods in the U.S. *Regulatory Toxicology and Pharmacology* 46:18–22, 2006.

have a comprehensive and clearly articulated five-year plan. The FYPWG suggests that the Plan identify the criteria for prioritization that apply to each of the priority areas. In addition to those criteria identified by ICCVAM agencies, we suggest the identification of endpoints for which partial or full replacement of animal use is achievable in the near-term. Please note the ILSI/HESI proposal (Carmichael et al., 2006)² and the HSLF comments.

Is the Draft Five-Year Plan Strategic?

While appreciating the difficulty in assembling information from 15 federal agencies, the FYPWG feel the Draft Five-Year Plan falls short in articulating a clear vision and strategic perspective. Although some strategic objectives are articulated, in some ways, the Draft Five-Year plan reads more like a catalogue of activities rather than a plan. It appears to be a mix of strategic objectives and opportunistic objectives. What is the overall strategic vision? Where will ICCVAM/NICEATM be at the end of five years? The FYPWG appreciates the difficulty entailed in articulating a vision and strategy that cuts across 15 federal agencies. But, in considering the charge from Congress, we feel it is just such a vision and strategy that has been requested by the congressional report language. Focus on the 2-3 highest priority areas that cut across the ICCVAM agencies and develop a detailed plan to carry them out with near-term and far-term goals.

By taking a strategic view, the Five-Year Plan may be able to identify procedural challenges as well as scientific challenges. The FYPWG understands that some perceive the current ICCVAM validation process as too expensive, time-consuming, and a very high hurdle for alternative methods. As part of the Five-Year Plan, would it be beneficial for ICCVAM/NICEATM to consider opening up a dialogue with the scientific, stakeholder, and regulatory communities to see if there may be ways to utilize more streamlined processes that do not sacrifice scientific rigor?

Is the Draft Five-Year Plan Detailed with Clearly Defined Priorities and Milestones?

The FYPWG believes that there is a compelling need to consider revising the Draft Five-Year Plan to assure that there are clearly defined priorities with timelines or milestones. While it may be ideal to have such detailed plans for all of the priorities, this may not be practical at this time. We suggest it may be beneficial to consider a SWOT-type of analysis that would cover strengths, weaknesses, opportunities, and threats. Given the activities in Europe, it is important to take advantages of such opportunities afforded, but the Five-Year Plan should not just be opportunistic. It should provide a clear “road map” for NICEATM/ICCVAM to identify the highest priority objectives, to plan to achieve these objectives, and to make real and lasting impacts across the federal government on the development, validation, and adoption of new, revised, and alternative assays.

² Carmichael NG, Barton HA, Boobis, AR, Cooper RL, Dellaraco VL, Doerr NG, Fenner-Crisp PA, Doe JE, Lamb JC, Pastoor TP, Agricultural Chemical Safety Assessment: A multisector approach to the modernization of human safety requirements. *Critical Reviews in Toxicology* 36:1-7, 2006.

As it stands right now, the activities of NICEATM/ICCVAM appear to be governed by a “first come/first served” process rather than by a process designed to achieve results with the greatest impact or to assign limited resources based on the highest priority issues.

Does the Draft Five-Year Plan Describe Clearly Defined Roles?

It was difficult to discern the roles and responsibilities of ICCVAM, NICEATM, and the other organizations (e.g., individual agencies) in the Draft Five-Year Plan. Given that the report is a Five-Year Plan for NICEATM/ICCVAM, it should emphasize what NICEATM/ICCVAM itself can carry out or strongly influence. Furthermore, it would be very helpful in addressing the request of the congressional report language, to consider revising the Draft Plan to include more details, at least for the select set of highest priorities that speak to the specific elements of research and development, translation, and validation. One suggestion is to use a tabular format as shown below to map out the roles of each agency and committee.

Activity	R&D Lead Agency	R&D Timeline	Translation Lead Agency	Translation Timeline	Validation Lead Agency	Validation Timeline
Method						

Does the Draft Five-Year Plan Clearly Identify the Gaps?

The Draft Five-Year Plan does a good job in articulating what is being done in terms of research and development efforts of the federal agencies that comprise ICCVAM. However, the Draft Plan does not clearly focus on the gaps that appear to exist along the path that starts from research and development, proceeds through translation (standardization), then onto validation, and finally adoption by the regulatory agencies and integration into their testing frameworks. Since the ICCVAM Authorization Act of 2000 requires validation, the Five-Year Plan needs to ask, “What are the gaps along the method-development, validation, and adoption paths?” It is the impression of the FYPWG, based on the information provided in the Draft Five-Year Plan, that while there are considerable research activities focused on development of new and novel methods, there are currently very few activities focused on translation and still fewer on validation.

The focus for the current federal funding seems to be for basic research; therefore, new, revised, and alternative methods will continue to have a very difficult time making it from the researcher’s bench into a regulatory testing regimen. Formal validation is a necessary step that must be achieved for a test method to be adopted and used in a regulatory program – so this raises the question, “Are there gaps that exist in the planning (or lack of planning) for these validation activities?” If so, the Five-Year Plan should identify these gaps. Furthermore, even if translation and validation studies were given greater attention, without a strategic plan in place, NICEATM and ICCVAM agencies will not have a clear path forward to devote to focusing these activities on the highest priority methods or areas.

In addition, the FYPWG believes it is incumbent upon the ICCVAM agencies themselves – as critical stakeholders – to fully embrace the 3Rs and exert the leadership needed to assure that the validated methods delivered by the efforts of NICEATM and ICCVAM are actualized into regulatory testing frameworks as soon as practicable. The FYPWG suggests that the Plan include a table of past methods reviewed and approved by ICCVAM and the agencies’ actions on those tests. Using this table, it can help identify gaps or barriers for current or future methods. If so, consideration should be given to addressing this as part of the Plan.

Does the Draft Five-Year Plan Address Communicating with and Engaging Stakeholders?

With respect to the Plan itself, the FYPWG believes that the report could be strengthened by including more consideration of ways to both engage and communicate with stakeholders. Education, training, and communication with stakeholders are the keys to success. There are many different stakeholders, each with unique and valuable perspectives. NICEATM is to be complimented for its outreach efforts to engage stakeholders in review and comment on the Draft Five-Year Plan.

The unique organizational structure of ICCVAM as a coordinating committee of 15 federal agencies means that NICEATM shoulders considerable burden in dealing with stakeholders. Yet in some, if not many instances, the stakeholders’ concerns really lie not with NICEATM, but with one or more of the ICCVAM agencies. The FYPWG is aware that concern with slow progress in incorporating new, revised, and alternatives methods into regulatory testing frameworks has frustrated many stakeholders. By including specific elements in the Five-Year Plan to reach out to and engage stakeholders, ICCVAM and NICEATM will go a long way toward developing the foundation needed for success.

FYPWG Review - Specific Comments:

- 1) U.S. interagency coordination and national acceptance and partnership are critical. These should stand out in the Plan as the primary focus.
- 2) The Plan should give more attention to NICEATM/ICCVAM complementing without duplicating international R&D and validation efforts. Note HSLF comments.³ NICEATM/ICCVAM needs to take better account of complementing international efforts and fast-tracking approved methods, as appropriate within U.S. priorities.
- 3) In regard to the databases and compiled information, how can system developers be integrated better into the program?
- 4) It may be useful for the report to consider addressing procedural as well as scientific challenges. Concern with the current ICCVAM validation process (see above “Is the Draft Five-Year Plan Strategic?”) presents both challenges and opportunities.

³ Public comments submitted by Sara Amundson, Humane Society Legislative Fund, on behalf of the Doris Day Animal League, Humane Society Legislative Fund, The Human Society of the United States, People for the Ethical Treatment of Animals, and the Physicians Committee for Responsible Medicine in response to the Federal Register notice (71 FR 66172, available at <http://iccvam.niehs.nih.gov/docs/StrPlnPubCmts.htm>)

Exploration of more streamlined processes that do not sacrifice scientific rigor should be considered for incorporation into the Plan. Also, to be most effective, the expert panels convened to review the validation status of test methods under review need to be thoroughly briefed on their charge and duties.

- 5) The plan does not detail the gathering and use of human data to improve evaluations of test method relevance. According to the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC, 2004),⁴ it is recommended that human data should be more often used for risk assessment, since they form the most direct evidence for human health risk. It is also recommended that if sufficient quality human data, as well as animal data, are available, the human data should be given priority regardless of their effect on the risk assessment. The same could be said of the use of human data for validation purposes. Indeed, it was a consensus recommendation of the 2002 OECD Conference on Validation and Regulatory Acceptance of New and Updated Methods in Hazard Assessment that an international expert workshop be convened to: (a) identify sources of existing, high quality human data (e.g., occupational biomonitoring, clinical trials, accidental exposure/poison control, epidemiology, etc.); (b) discuss the existence/creation of centralized databases, toxicity endpoints covered, data quality issues, etc.; (c) develop consensus positions and recommendations for moving forward; and (d) implement a system of reporting and tracking all vertebrate animal use for regulatory testing purposes. Regrettably, in the nearly five years since the OECD validation conference, no perceptible effort has been made on the part of regulatory authorities or industry to implement this recommendation. ICCVAM and its member agencies are invited to take a leading role in the organization of an international workshop on this topic.
- 6) For the priority tests chosen, describe the 3R impacts, and, where possible, provide quantitative estimates.

Additional comments and questions raised by the FYPWG about information in the Draft Five-Year Plan are presented in Appendix 1.

FYPWG presented its report to SACATM at its meeting on June 12 and it was unanimously accepted. The minutes from that meeting (Attachment 1, under preparation) cover the breadth of the discussion on the draft NICEATM/ICCVAM Five-Year Plan and should be viewed with weight equal to the FYPWG report.

⁴ Money CD. The use of human experience data in the EU risk assessment process. *Risk Analysis* 27:387-397, 2004.

Appendix 1

The FYPWG has additional comments or questions about the information presented in the following lines in the Draft Five-Year Plan.

The 3Rs are typically presented in the order: replacement, reduction, and refinement. It would be good to follow this order consistently throughout the document.

Line 19: “Large” numbers-this seems a bit ambiguous, too vague.

Line 43: Who is the target audience for workshops?

Line 46: How will partnerships be developed?

Line 79: Insert second to the last line-why the use of the word “injury” versus pain?

Lines 79-87 and their two associated text boxes (on U.S. laws that require alternatives to be considered): This information can be deleted as not critical to the report.

Line 86: “one” to an

Line 182: Are there examples to cite? What is the use rate of the new UP Procedure? Is it being accepted and used nationally?

Line 255-257: Is the substantial reduction in pain due to less animals being used or another factor of the LLNA? The sentence is not clear.

Line 261: The radioactive materials line seems to float. If use of radioactive materials is expected to cause pain and distress, it should be stated.

Line 266-285: EPA was mandated by Congress, not other agencies. Need to acknowledge EPA sponsored ICCVAM RBA assays. ER Japanese assay – is this a priority for EPA? or another U.S. agency? If not, why would this be a priority for ICCVAM?

Line 269, Page 16 mid-insert: “*such guidance facilitates the acceptable....*” A guidance document will help *direct* the work and ensure that it is performed in an acceptable manner.

Line 299-317: Under Chronic Toxicity/Carcinogenicity, what role is there for NICEATM/ICCVAM in FDA and NIEHS to “seek alternative models”? Advice on translation and validation sorely needed (recall transgenic models). For the Comet assay, why is this a priority? For what U.S. agency is this assay a priority? Are there sufficient genotoxicity assays already?

Line 298: Pertaining to the phrase “will revisit the validation,” what does this mean? What is the next step?

Line 318-328: Under “Other Toxicity Areas of Interest,” “Neurotoxicity,” what about work of EPA and CAAT? Under “Reproductive and Developmental Toxicity,” what about the work of EPA on the ILSI ACSA 1-gen as referenced by Cooper, RL, Lamb, JC, Barlow, SM, Bentley, K, Brady, AM, Doerr, NG, Eisenbrandt, DL, Fenner-Crisp, PA, Hines, RN, Irvine, LFH, Kimmel, CA, Koeter, H, Li, AA, Makris, SL, Sheets, L, Speijers, GJA, and Whitby, K. 2006. A tiered approach to life stages testing for agricultural chemical safety assessment. *Critical Reviews in Toxicology* 36, 69-98. (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16708695&query_hl=9&itool=pubmed_docsum) This appears to be a priority for EPA. In addition, what about the recent ILSI HESI workshop on Alternative Assays for Developmental Toxicity as referenced by this weblink: <http://www.hesiglobal.org/Committees/TechnicalCommittees/DART/HESIAltAssayPresentations.htm>?

Line 333-334: Which “new approaches/ test methods” will likely be ready for use more quickly?

Line 336-337: Although there is a claim that NICEATM and ICCVAM are involved in “linking R&D to standardization and validation,” this “linkage” is not described for each method discussed. This is important because without engagement, much early work may need to be redone.

Line 350-351: There is a lack of specifics for the activities of NICEATM and ICCVAM with respect to the National Toxicology Program (NTP) High Throughput Screening (HTS). The NTP’s Roadmap states “*Activities and assays developed under the NTP Roadmap will be done in cooperation and consultation with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to maximize their value to regulatory agencies.*”

Line 363-368: Statements such as “*NICEATM and ICCVAM will monitor progress with this test model, evaluate the validation status of promising tests with regulatory applicability, and make recommendations for regulatory acceptance*” lack needed specificity.

Line 369-375: What assays are being referred to as “EPA developing assays to evaluate fish and amphibians ... and validating an assay in amphibians”? Are these EPA’s EDSP assays? Do these assays include the Frog Metamorphosis assay? If so, is there coordination with EPA? Does EPA need/want ICCVAM’s help?

Line 380-396: In regards to ToxCast, what are the roles of NICEATM and ICCVAM? Before its implementation, isn’t there a need for validation? Is there a need for early consultation to provide feedback on scope of “translation” and validation? In addition, what is ATSDR specifically doing? Their activities are not specified here.

Line 397-418: Under “Biomarkers,” please give an example of a clinical biomarker, such as prostate specific antigen (PSA)? In line 415, the phrase “other biomarkers are

undergoing standardization and validation” does not specify who is doing this? When? What is ICCVAM’s role? Has there been input into the validations plan?

Line 419-431: Under “Nanomaterials Testing,” there are no real specifics. What role has been given to ICCVAM from the lead agencies?

Line 432-454 Under “Toxicology Databases,” the coordination of these activities seems to be a good role for ICCVAM. What efforts will be made to check the quality of the database information?